June 30, 2005

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398

Tel. 919 483 2100
www.gsk.com

Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: NAS 0; Not Product Specific
Response to FDA Request/Comment: Comments on FDA Drug-Diagnostic Co-Development Concept Paper
[DOCKET NO. 2004N-0279]

Dear Sir or Madam:

On April 8, 2005, the Food and Drug Administration (FDA) issued a Concept Paper on Drug-Diagnostic Co-Development and requested public input as per the Docket Number above. The concept paper outlines the Agency's preliminary thinking for how to prospectively co-develop a drug or biological therapy and device test in a scientifically robust and efficient way. The concept paper is intended to promote discussion prior to subsequent development and issuance of a draft guidance for public comment.

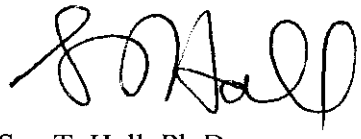
GlaxoSmithKline (GSK) welcomes the opportunity to comment on FDA's Concept Paper. GSK is one of the world's leading research-based pharmaceutical and biotechnology companies. Our company is dedicated to discovering and developing medicines that allow patients to lead longer, happier, healthier, and more productive lives.

Advances in genetic research are now opening up new horizons in the understanding of the science behind the variability between individuals. Utilization of pharmacogenetics and pharmacogenomics is expected to significantly contribute to the development of better medicines for populations and targeted therapies with improved benefit/risk ratios for individuals. GSK is using information gleaned from the human genome throughout the drug discovery and development process to identify novel ways to combat disease. We are actively engaged in the research to provide safer and more effective medicines.

Because of our significant interest in this topic, enclosed are specific comments submitted on behalf of GlaxoSmithKline. In addition, as members of the Pharmaceutical Research and Manufacturers of America (PhRMA), GSK has contributed to the comments on this concept paper submitted by PhRMA and we are generally in agreement with those comments.

Comments have been posted to Docket No. 2004N-0279. If you have any questions regarding these comments, please contact me at (919) 483-6159. Thank you.

Sincerely,



Sue T. Hall, Ph.D.
Director
U. S. Regulatory Affairs

COMMENTS ON FDA DRUG-DIAGNOSTIC CO-DEVELOPMENT CONCEPT PAPER [DOCKET NO. 2004N-0279]

OVERALL COMMENTS

On April 8, 2005, the Food and Drug Administration (FDA) issued a Concept Paper on Drug-Diagnostic Co-Development and requested public input as per the Docket Number above. The concept paper outlines the Agency's preliminary thinking for how to prospectively co-develop a drug or biological therapy and device test in a scientifically robust and efficient way. The concept paper is intended to promote discussion prior to subsequent development and issuance of a draft guidance for public comment.

The unravelling of the human genome and advances in genetic research are now opening up new horizons in the understanding of the science behind the variability between individuals. Utilization of pharmacogenetics and pharmacogenomics is expected to significantly contribute to the development of better medicines for populations and targeted therapies with improved benefit/risk ratios for individuals. GlaxoSmithKline (GSK) is a leader in the conduct of pharmacogenomic research to provide safer and more effective medicines for patients. We applaud FDA for the activities undertaken to provide a regulatory framework for the utilization of this technology in drug development and also for their willingness to partner and work with Industry to develop appropriate guidances.

The ongoing dialogue between Industry and FDA and activities such as the recent joint workshop that included discussion of the concept paper are welcomed and supported. It is hoped too that FDA will continue to liaise globally for a harmonized approach that is supported by all major regulatory agencies given the potential global regulatory impact of pharmacogenomics on drug development.

GSK appreciates the issuance of the concept paper to begin to address the many complex issues pertaining to the co-development of drugs and diagnostics. We believe that the concept paper provides a reasonable starting point for discussion but we also consider that there are significant opportunities for modifications to be incorporated to provide a workable framework for the drug-device co-development process.

The areas where GSK advocates revisions to the guidance are summarized in this document.

GENERAL COMMENTS

GSK supports the issuance of a guidance regarding the co-development of pharmacogenomic tests and drugs to ensure that an appropriate and consistent framework is established through the provision of a clearly delineated process. Such a process should also facilitate the goal of simultaneous review and approval of drug and test so that medicines of value to the prescribing community and the patient can reach the marketplace in an efficient and timely manner.

GSK believes that the concept paper focuses on many of the salient issues but would also suggest some revisions particularly with regard to the proposals pertaining to:

- biomarker identification and subsequent test development activities - GSK believes that there needs to be consideration of this occurring during phase II/III of the clinical development program rather than solely prior to ph II

- role and acceptability of retrospective analyses - GSK considers this a critical component of the regulatory decision making process for pre- and post-registration

- the requirements for clinical evaluation in a test-negative population (assessment, study design etc) - GSK would propose that this be addressed on a case-by-case basis, being dependent upon potentially a number of factors including whether safety or efficacy is the consideration, the risk:benefit profile of the drug and the role of the test in the established standard of care

Additionally, it needs to be noted that not all pharmacogenetic and pharmacogenomic applications to safety and efficacy will result in a co-developed test. Further, there also needs to be the recognition that convergence of clinical utility and regulatory decision-making drivers such that there is agreement that a drug-device co-development program is warranted may occur at many different points along the drug development continuum.

SPECIFIC COMMENTS

SECTION 1: INTRODUCTION, BACKGROUND AND SCOPE

- It is unclear if the scope includes the optional use of an in vitro diagnostic for decision making about drug selection for patients in clinical practice – GSK would suggest that this scenario should be in scope of the document.
- Figure 1 does not depict what GSK sees as a more common scenario whereby emerging data from phase II or phase III studies constitute the impetus for

consideration and potential development of a biomarker to select patients. Also, it would be helpful for FDA to indicate where they see any differences in the key steps for an NCE vs. marketed product.

- It would be helpful for FDA to additionally clarify their recommendations pertaining to specifically "homebrew" assays.
- A likely common occurrence is for multiple diagnostic tests to be developed e.g. improved diagnostic test availability - the associated processes and activities need to be addressed in the guidance.
- It would be helpful if FDA provided specific examples in the document pertaining to analytic validity, clinical validity and clinical utility to assist in the definitions and further illustrate the concepts.

SECTION 2: REVIEW PROCEDURE ISSUES

- Figure 2: comment as for Figure 1.
- Given the complexity of the aspects to be addressed for a drug-diagnostic co-development program, GSK requests that FDA consider additional opportunities for Sponsors to solicit binding input from the Agency, for example, Special Protocol Assessments.
- GSK requests that FDA specifically address the scenario whereby a Sponsor may initially utilize the VGDS process prior to regulatory decision-making drug development activities for a drug-diagnostic co-development program.
- It would be helpful for FDA to expand on the option for 'sequential' approval as noted in 2.2 (7).
- The guidance should address specific aspects pertaining to product labelling for both pre- and post-registration activities.

SECTION 3: ANALYTICAL TEST VALIDATION

- GSK would urge FDA to ensure that a globally consistent recommendation be made for sample storage/banking, especially given the current activity of the EMEA with regard to this aspect.
- GSK would submit that a sponsor may not be in a position to design a phase III study (for clinical validation and utility assessment) based on biomarkers discovered in phases I/II since the larger trials may be required to determine the markers associated with a given response. GSK requests that FDA consider this scenario in its recommendations.

SECTION 4: PRECLINICAL PILOT FEASIBILITY STUDIES

- In section 4.2, the premise appears to be that the basic observation upon which a test result will be based is a continuously varying parameter. However, for pharmacogenetics specifically, the test result will be based on genotype and it would be helpful if the document specifically highlighted recommendations for this scenario.
- Similarly, in section 4.4, the Receiving Operating Characteristics analysis discussed pertains only to a continuous variable (e.g. expression level), not for a test based on genotype or on a set of genotypes; FDA is requested to clarify.

SECTION 5: GENERAL APPROACHES TO DEFINE CLINICAL TEST VALIDATION

- It is not clear if FDA is suggesting that if a study features an 'enriched' sample, that meaningful estimates of NPV and PPV cannot be derived – GSK would propose that an estimate of PPV and NPV can be made for 'generalizability' to clinical practice as a function of the sensitivity and specificity observed in the study sample and by assuming a specific prevalence of cases in an unselected population (also applicable to Addendum C).

SECTION 6: CLINICAL UTILITY

- This section should further address the scenario where a definitively identified predictive pharmacogenetics marker (or set of markers) will not have occurred to the point that a phase III clinical program can be specifically designed as a consequence.
- For section 6.2, this section should be expanded to include discussion of additional aspects that need to be considered such as what comprises 'clinical utility' and potential differences for safety vs. efficacy considerations and marketed products vs. NCEs.
- FDA is requested to clarify the scenarios for potential evaluation in a test-negative population and implications for 'off label' usage - GSK would propose that this be addressed on a case-by-case basis, being dependent upon potentially a number of factors including whether safety or efficacy is the consideration, the risk:benefit profile of the drug and the role of the test in the established standard of care
- FDA is requested to clarify the recommendations for the role and acceptability of retrospective analyses for the validation of markers - GSK considers this a critical component of the regulatory decision making process for pre- and post-registration.
- As with all research, consents should cover the intended scope; however, GSK considers that requirements for overly specific details in consents may hamper

innovation and would urge FDA to recognize the rigorous coding and handling mechanisms already used and further, given that these are outlined by the EMEA too, that this also constitutes a facilitatory global framework.

ADDENDUM

- Addendum A - GSK would propose an additional aspect: Evidence should be provided that the ruggedness of the device has been studied in a systematic fashion. Ruggedness refers to the ability of the device to give reproducible results even when slight deviations from recommended conditions are used in operating the device. In the event that deviations cannot be tolerated for some factors, then this should be clearly defined in the operating instructions, and allowable tolerances should be specified.